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Focused ultrasound combined with radiotherapy for malignant brain tumor: a preclinical and clinical study

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Abstract

Introduction: Blood-brain barrier (BBB) remains to be the major obstacle to conquer in treating patients with malignant brain tumors. Radiation therapy (RT), despite being the mainstay adjuvant modality regardless of BBB, the effect of radiation induced cell death is hindered by the hypoxic microenvironment. Focused ultrasound (FUS) combined with systemic microbubbles has been shown not only to open BBB but also potentially increased regional perfusion. However, no clinical study has investigated the combination of RT with FUS-BBB opening (RT-FUS).

Methods: We aimed to provide preclinical evidence of RT-FUS combination in GBM animal model, and to report an interim analysis of an ongoing single arm, prospective, pilot study (NCT01628406) of combining RT-FUS for recurrent malignant high grade glioma patients, of whom re-RT was considered for disease control. In both preclinical and clinical studies, FUS-BBB opening was conducted within 2 h before RT. Treatment responses were evaluated by objective response rate (ORR) using magnetic resonance imaging, progression free survival, and overall survival, and adverse events (AE) in clinical study. Survival analysis was performed in preclinical study and descriptive analysis was performed in clinical study.

Results: In mouse GBM model, the survival analysis showed RT-FUS (2 Gy) group was significantly longer than RT (2 Gy) group and control, but not RT (5 Gy) group. In the pilot clinical trial, an interim analysis of six recurrent malignant high grade glioma patients underwent a total of 24 RT-FUS treatments was presented. Three patients had rapid disease progression at a mean of 33 days after RT-FUS, while another three patients had at least stable disease (mean 323 days) after RT-FUS with or without salvage chemotherapy or target therapy. One patient had partial response after RT-FUS, making the ORR of 16.7%. There was no FUS-related AEs, but one (16.7%) re-RT-related grade three radiation necrosis.

Conclusion: Reirradiation is becoming an option after disease recurrence for both primary and secondary malignant brain tumors since systemic therapy significantly prolongs survival in cancer patients. The mechanism behind the synergistic effect of RT-FUS in preclinical model needs further study. The clinical evidence from the interim analysis of an ongoing clinical trial (NCT01628406) showed a combination of RT-FUS was safe (no FUS-related adverse effect). A comprehensive analysis of radiation dosimetry and FUS energy distribution is expected after completing the final recruitment.

Keywords: Brain metastasis; Focused ultrasound; Malignant glioma; Radiation therapy; Stereotactic radiosurgery.